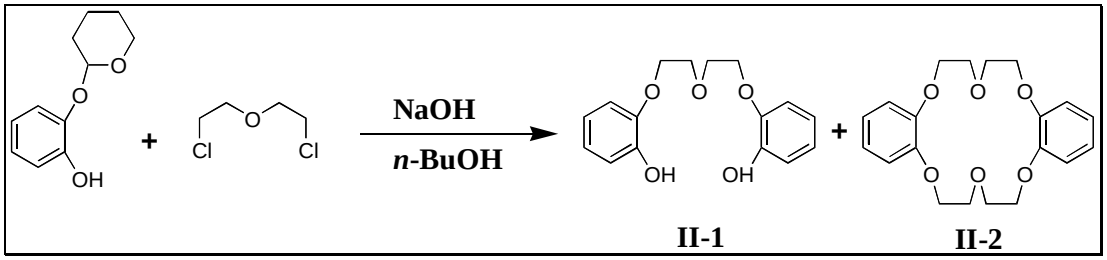
Chapter II

Crown Ethers

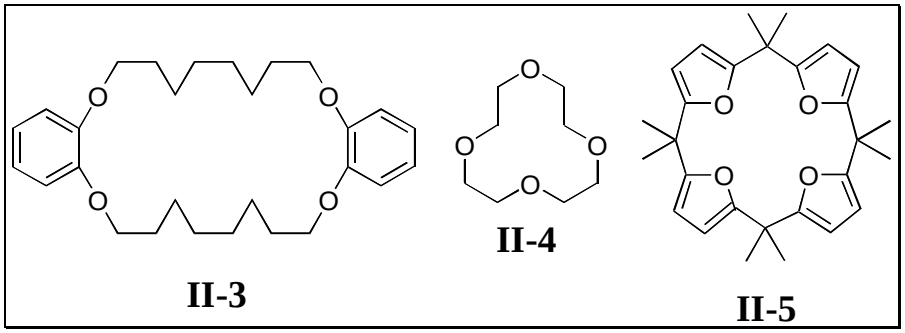
II.1 Introduction

The major historical advance of crown ether use by chemists began in 1967 when Charles Pedersen synthesized dibenzo-18-crown-6 (**II-2**).[1,2] The synthesis was purely accidental since his intended synthetic target was the open-chained diphenol **II-1**. It was actually Pedersen's discovery that crown ethers formed complexes with alkali metals that started the scientific community's interest in crown ethers (see Chapter I).[3] He is credited with opening the eyes of chemists to the area of supramolecular and host-guest chemistry.[4,5] Several reviews have been published that discuss the origins and discoveries concerning crown ethers.[3,6-11] There were, however, other reports alluding to the synthesis of crown ethers or closely related cyclic molecules prior to his Nobel Prize winning discovery.



In 1937, Lüttringhaus wanted to make molecules that concatenate, maybe having unusual properties. He made several macrocycles similar to **II-3**, but they lacked sufficient donor groups for complexation.[12-15] In the mid-1950s, Stewart, Wadden, and Borrows performed cyclo-oligomerizations of ethylene oxide and made several macrocyles having structures similar to **II-4**.[16] They noted that the cyclic ethers had interesting properties, but failed to investigate the properties extensively. A final example

of the history before the dawn of crown ethers involves the furan-acetone tetramer **II-5**. Ackman, Brown, and Wright analyzed this compound and several others having similar structure.[17] They called them ‘anhydrotetramers’ because the molecular formula could be written as four acetones and furans minus four water molecules.



The original definition of a crown ether, as reviewed by Bradshaw, was "those compounds with multiple ether oxygen atoms incorporated in a macrocyclic backbone."[6] However, today the definition has expanded to include macrocycles with other donor groups such as sulfur, nitrogen, and other heteroatoms. Crown ethers with nitrogen and sulfur donor groups have been given the more specific names azacrown and thiacrown ethers, respectively. The origins of the nomenclature for crown ethers came from Pedersen’s observations. He noticed that if he modeled the complex between a potassium ion and **II-2** using Corey-Pauling-Koltun (CPK) models the macrocycle 'crowned' the potassium ion 'much as a regal crown adorns a monarch's head.'[3] He chose to use the word ‘crown’ in his nomenclature. As an example, structure **II-4** is designated 12-crown-4, the numbers indicating the number of atoms in the macrocycle and the number of heteroatoms, respectively.

Traditionally an ethylene-oxy group has been the cyclic repeat unit, but others have been used. There are several reasons ethylene-oxy repeat units have been used in crowns. They are: i) flexible units, ii) can have relatively strain free conformations, i.e. they can adopt the all gauche conformation that permits easy alignment of the donor

group electron pairs, iii) easily available commercially, iv) historically been the usual repeat unit.[3] The second reason is probably the most important from a supramolecular chemist's point of view since the donor group alignment is crucial for self-assembly.

Other repeat units used in crown ethers include aromatics, benzylics, methylenes, and others. The most common substitute for the ethlyene-oxy repeat unit is the *ortho*-phenylene or benzo unit since it has the same number of carbon atoms. The incorporation of aromatic groups increases the rigidity of the crowns as well as their crystallinity. However, they typically have lower binding constants mainly due to the lower basicity of the electron pairs of the phenolic oxygens. The phenolic oxygens are sp^2 hybridized, rather than sp^3 as in the ethylene-oxy units. As an example, the effect of replacing one ethylene-oxy with a catechol group reduces the binding constant of 18-crown-6 with the *t*-butlyammonium cation by over 50-fold (**Figure II-1**).[18]

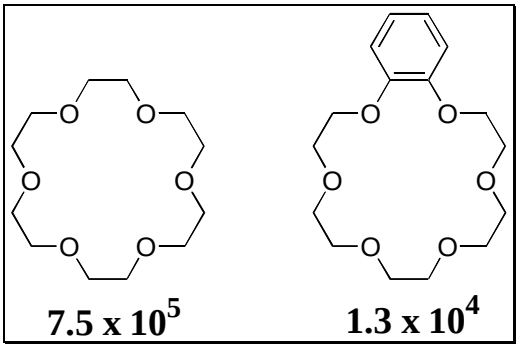


Figure II-1. Comparison of binding constants for 18-crown-6 (left) and benzo-18-crown-6 (right).[18]

Incorporation of phenylene groups allows a relatively simple method for the functionalization of crown ethers. Several functionalized crowns have been synthesized and used extensively in our labs.[19-49]

As mentioned above, research surrounding crown ethers has focused on their binding properties. This is primarily due to their polarity.[50] Crown ethers have what is termed a universal solubility. The type of solvent they are dissolved in, either hydrophilic or lypophilic, determines the conformation of the crown ether (**Figure II-2**). 18-Crown-6,

depending on the medium, directs its ether oxygens either inside (for lipophilic media) or outside (for hydrophilic media). On the scale of lipophilicity values, crown ethers are exactly zero.[51] They exhibit a perfect balance between hydrophilic and lipophilic behavior.

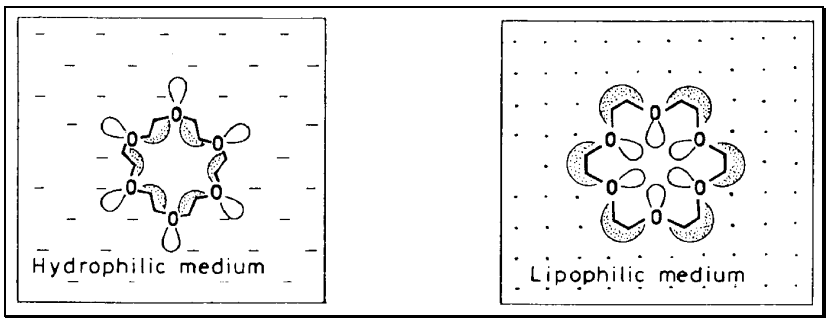


Figure II-2. Comparison of the conformations of 18-crown-6 in hydrophilic and lipophilic medium.[50]

The typical methods employed for the synthesis of crown ethers (**Figure II-3**) surprisingly have not changed much since Pedersen introduced them in 1967.[1,2] All of the methods, except the last, use the Williamsen ether synthesis in the cyclization step. Using the tosylate leaving group instead of the chloride has increased the yields for many of the crowns, but this results in an extra reaction step and the tosylates are not easily stored.

The yields for the cyclization steps can be increased by several methods. The most used method is the high-dilution method. Ruggli, in 1912, developed the concept of the high-dilution technique for cyclizations.[52] He stated that the intramolecular ring closure reaction is first order and its rate is proportional to concentration. The intermolecular condensation reaction (polycondensation) is second order and its rate is proportional to the square of concentration. Therefore, dilution favors the intramolecular cyclization. The initial theoretical analysis for high-dilution reactions was established as early as 1934.[53-56] Ziegler established the first experimental methods for high-dilution reactions and used them abundantly.[57] Two contrasting factors influence the cyclization

step: a) the low tendency for medium or large ring formation, and b) the reaction towards oligomeric chains.[58] For 5 to 6 membered rings, intramolecular cyclization is faster than oligomerization, the reverse is true for higher ringed systems, but high dilution makes it more probable. This effect is known as the Ruggli-Ziegler dilution principle.

Dye et al. developed an alternative to the high-dilution method.[59] They used a flow cell like that used in fast kinetic studies and reduced the reaction time and amount of dilution considerably. Jurczak and co-workers synthesized azacrown ethers in almost quantitative yield using high pressure.[60,61]

The template effect is described as the complexation of a linear molecule, **A**, with some other molecule, **B**, usually an alkali metal, in a manner where the two reacting ends of **A** are arranged near each other. Therefore, the end groups of **A** are not easily available for the polycondensation reaction. The template effect is a method for cyclization that is highly appealing to the synthetic chemist. It eliminates the need for high dilution reactions and decreases the competing polycondensation reactions. The template effect is the reason Pedersen was able to synthesize dibenzo-18-crown-6.[3] It was actually Robin Greene at Dupont, Pedersen's colleague, that first applied the template term to macrocycle syntheses. Before Pedersen's discovery, Daryl Busch demonstrated the template effect for synthesis of all nitrogen macrocycles (cyclams) using transition metals. Also before Pedersen's discovery there was a previous report in 1907 when Braun and Tcherniac discovered the templated assisted synthesis of azamacrocycles. An example of this effect is shown in **Figure II-4**. The template effect was reported for the synthesis of benzo-27-crown-9 (catechol with octaethylene glycol ditosylate). The yield was 59% when t-Bu-OK was used as the base, 23% when guanidine was present, but only 2% when $HN=C(NMe_2)_2$ was present.[62] The unusually high yield of 18-crown-6 is due to the template effect with Na^+.[63]

Brietenbach, Boosfield, and Vögtle[58] describe three different types of template effects: (i) the *kinetic* template effect yields only a certain cyclic product if the template, either a metal or an organic molecule, is present,[63-65] (ii) the *thermodynamic* template

effect is due to formation of a stable complex between the template host and guest, shifting the equilibrium towards the cyclic product. The absence of the template results in a lower yield,[66,67] and (iii) the *equilibrium* template effect, a combination of both above effects, where the starting materials and the template form a reversibly stable intermediate complex.[68]

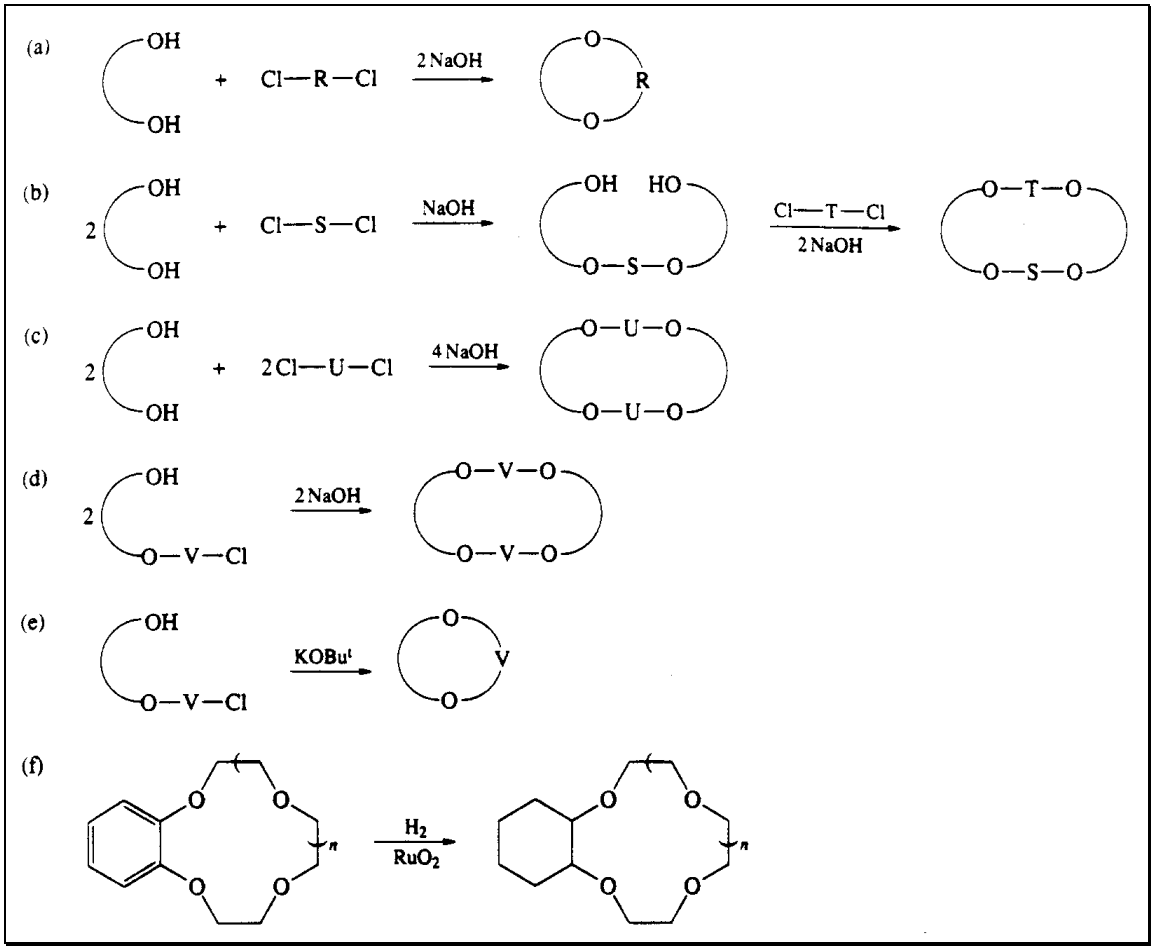


Figure II-3. Pedersen's synthetic methods for crown ether syntheses.[1,2]

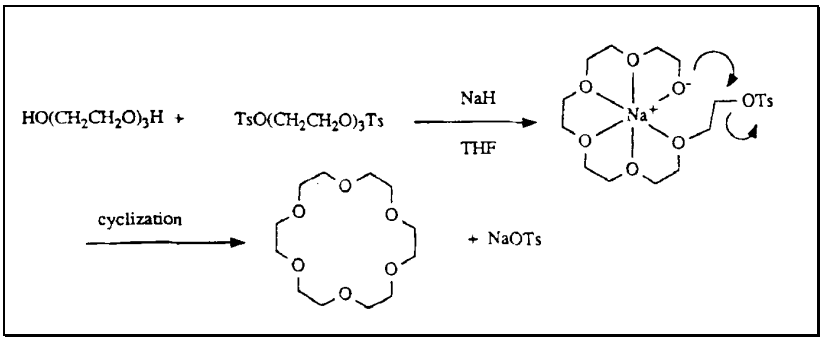


Figure II-4. Example of template effect for the synthesis of 18-crown-6.[3]

This chapter will discuss the synthesis and characterization of several phenylene-based crown ethers with and without functionalization. The typical method used for the synthesis (**Figure II-5**) is not one of the methods used by Pedersen, but is similar to reaction **b** (**Figure II-3**). The first step uses a large excess of the dichloride of ethylene glycol (**II-7**) to react with the bisphenol **II-6** giving the dichloride precursor **II-8**. The excess **II-7** was then removed by distillation and **II-8** was purified further by liquid-liquid extraction or flash column chromatography. The second reaction, the cyclization step, was a 1+1 Williamsen ether reaction between **II-9** and **II-8** and gave the desired macrocycle **II-10**.

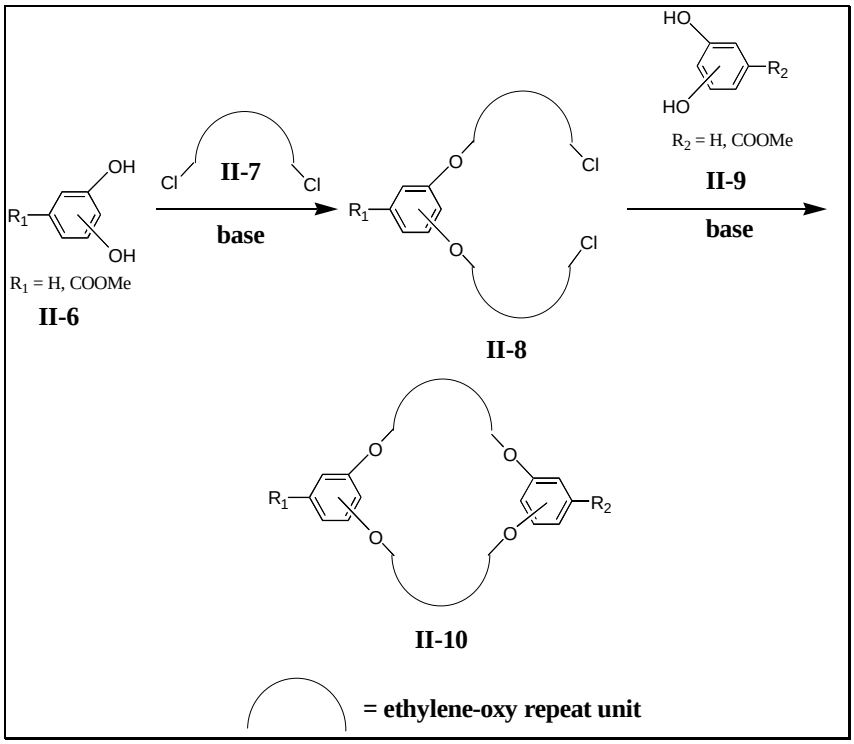


Figure II-5. Synthetic method for synthesis of phenylene-based crown ethers.

II.2 Results and Discussion

II.2.1 Bis(*meta*-phenylene)-26-crown-8

Bis(*meta*-phenylene)-26-crown-8 (**II-15**, **BMP26C8**) was synthesized from the dichloride precursor 1,3-bis(8-chloro-3,6-dioxa-1-octyloxy)benzene (**II-14**) and resorcinol, (**II-13**) (**Figure II-6**) using the pseudo-high dilution cyclization technique. Both **II-14** and **II-13** were dissolved in dimethylformamide (DMF) and added slowly (0.75 mL/h) to a mixture of potassium carbonate in a large volume of DMF at 110 ^{o}C. The reaction mixture was stirred for an additional five days after complete addition. The crown ether was isolated from a crude oil using Soxhlet extraction with ethyl ether. Recrystallization from ethanol resulted in a yield of 18.1% of **II-15**. The X-ray crystal structure of **II-15** is discussed in **Chapter V**.

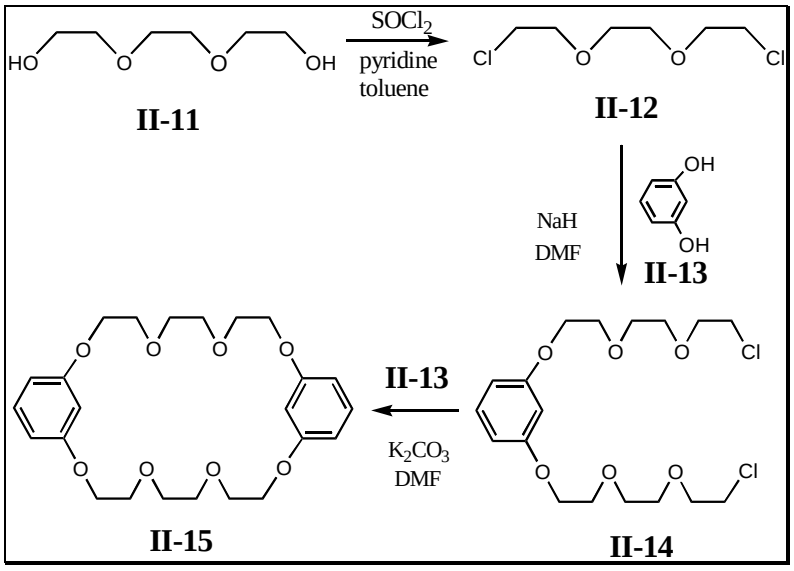


Figure II-6. Synthesis of bis(*meta*-phenylene)-26-crown-8, **II-15**.

The dichloride precursor **II-14** was synthesized in two steps. The first step was the synthesis of tri(ethylene glycol) dichloride (**II-12**) from tri(ethylene glycol) (**II-11**) using thionyl chloride and pyridine in toluene. The product was purified by distillation and the yield was 81.9%. In the next step a 10-fold mole excess of **II-12** was used to synthesize **II-14** using resorcinol (**II-13**). The dianion of **II-13** was generated first using

sodium hydride in DMF and was added to **II-12** in the absence of solvent. The unreacted dichloride **II-12** was removed by distillation and the resulting crude oil was purified by flash column chromatography. The yield of **II-14** was 94.3 %.

II.2.2 Mono-substituted Dibenzo-24-crown-8

The bis-*ortho*-substituted analog of **BMP26C8** is dibenzo-24-crown-8 (**DB24C8**). This crown ether is commercially available from Aldrich and Fluka. However, substituted **DB24C8** is not. The syntheses of several new mono-substituted derivatives of **DB24C8** are shown in **Figure II-7**.

The mono-ester of **DB24C8**, **II-19**, was an important target molecule. **II-19** was synthesized using two different methods. Both methods had similarities to the synthesis of **BMP26C8**; a solution of the unsubstituted dichloride precursor **II-17** and diphenol, methyl-3,4-dihydroxybenzoate[1] (**II-18**) was added slowly to a mixture of potassium carbonate in a large quantity of solvent at a set temperature. However, in the first method, **Method A**, DMF was used as the solvent and the addition rate was 0.60 mL/h. The reaction temperature was 110 ^{o}C. **II-19** was purified by Soxhlet extraction using ethyl ether and was isolated in a 35.5 % yield. For the second method, **Method B**, acetonitrile was used with an addition rate at 0.75 mL/h and a reaction temperature of 70 ^{o}C. **II-19** was purified as in the first method, but was obtained in a higher yield, 40.4 %.

The synthesis of the dichloride precursor **II-17** was conducted using two methods to optimize its overall yield. The first method, **Method A**, (**Figure II-8**) required two steps without the use of a large excess of tri(ethylene glycol) dichloride as needed in the second method, **Method B** (**Figure II-7**). For **Method A** commercially available 2-[2'-(2''-chloroethoxy)ethoxy]ethanol (**II-26**), was reacted with catechol (**II-16**) in acetonitrile in the presence of potassium carbonate at 70 ^{o}C. The reaction was monitored by ^{1}H NMR and was completed after 140 h with a yield of 90.4%. In the second step O,O-bis(8-chloro-3,6-dioxaoctyloxy)catechol (**II-17**) was synthesized using thionyl chloride and pyridine in toluene. The reaction mixture was refluxed for 36 h and the yield was 78.8%. Therefore, the overall yield of **II-17** using **Method A** was 71.2%.

[1] **II-18** was synthesized from 3,4-dihydroxybenzoic acid (see experimental).

Because of its high commercial cost of **II-26** it was also synthesized. An equimolar amount of thionyl chloride was added dropwise to a solution of triethylene glycol and pyridine in toluene. The reaction was heated to reflux for 20h. After work-up the desired product was isolated as an oil in a 42.0% yield.

For **Method B** (Step 1 of **Figure II-7**) a large excess of tri(ethylene glycol) dichloride (**II-12**) was added to a solution of **II-16** in acetonitrile in the presence of potassium carbonate. The product was isolated by liquid-liquid extraction using petroleum ether. The yield was 74.0 %. Based on the overall yields and materials' costs **Method B** appears to be the better of the two methods for the synthesis of the dichloride precursor **II-17**.

Once the mono-ester of **DB24C8** was produced the conversions of the ester functionality to the ester **II-22** and succinimide ester **II-25** were performed, both new compounds. To synthesize **II-22**, **II-19** was reduced to the alcohol **II-20** using lithium aluminum hydride (1 M solution in THF) in dry THF. The yield was high (94.2 %), resulting in a white crystalline powder. The product was recrystallized from ethanol.

The alcohol **II-20** was further converted to the isonicotinic ester **II-22** (a new compound) by way of condensation with the acid chloride **II-21**. **II-21** was synthesized in *situ* from the corresponding carboxylic acid. The carboxylic acid was stirred in a large excess of thionyl chloride under reflux for 1 h. The excess thionyl chloride was removed by vacuum distillation. A pyridine solution of the alcohol **II-20** was then added and the resulting mixture was heated at reflux. After work-up **II-21** was isolated in a 93.2 % yield.

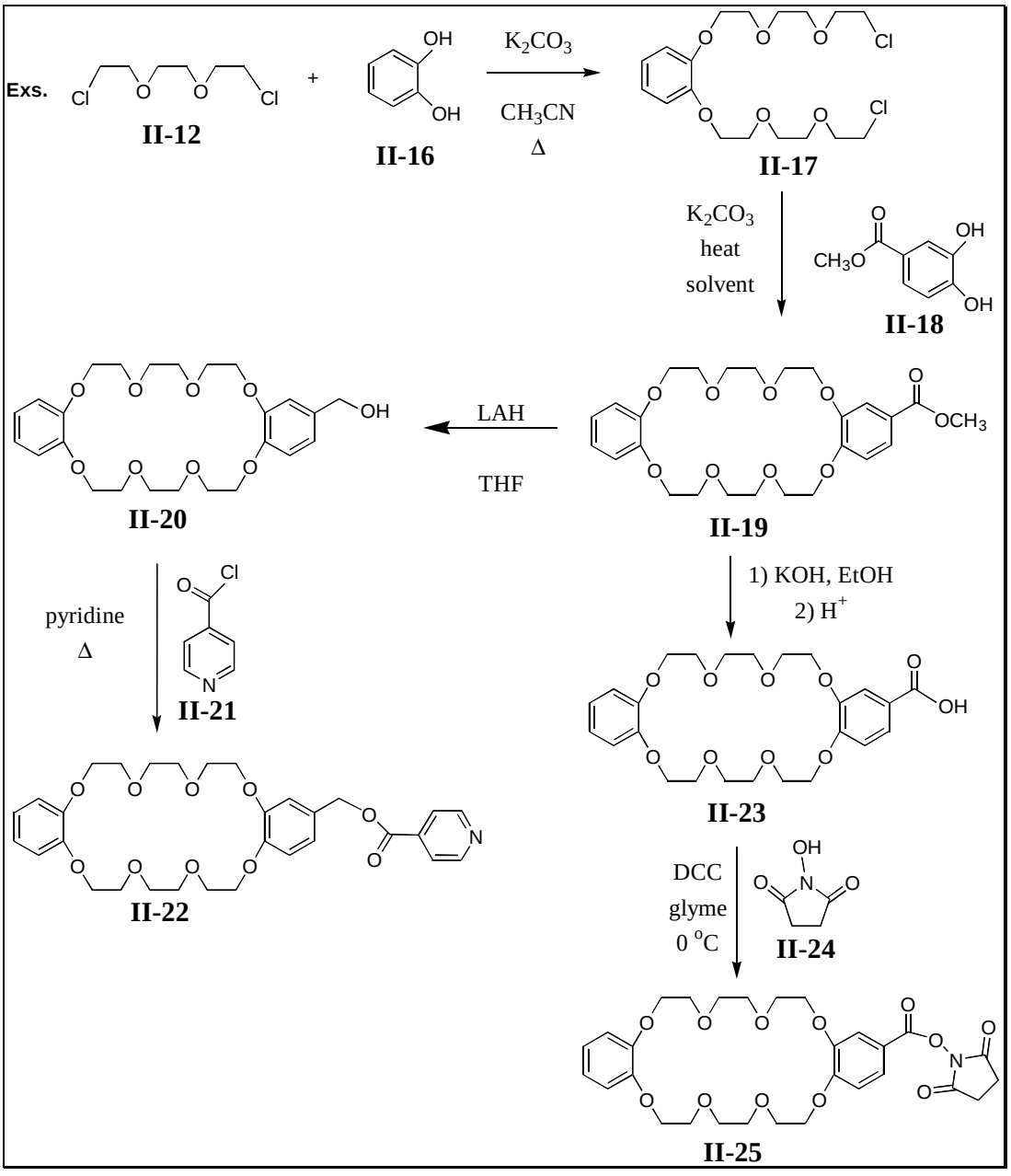


Figure II-7. Synthesis of various mono-substituted **DB24C8**s.

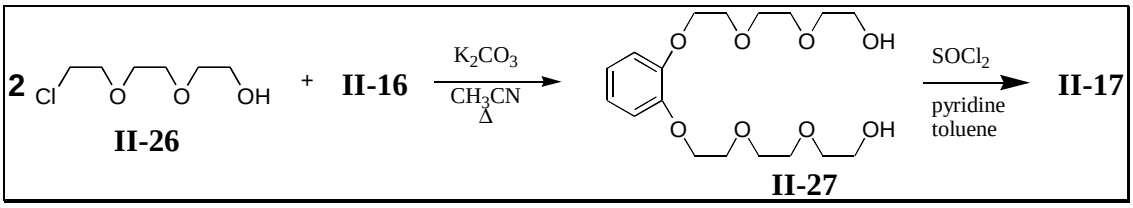


Figure II-8. Synthesis of **II-17** by **Method A**.

After the hydrolysis of the mono-ester **II-19** to the carboxylic acid **II-23 t**he succinimide ester of **DB24C8** (**II-25**) was synthesized. **II-25** was used for surface functionalization of poly(propylene imine) dendrimers. **II-19** was hydrolyzed in ethanol by potassium hydroxide (1 M). After neutralization **II-23** was isolated and recrystallized from chloroform/hexanes with a yield of 97.4 %. Conversion to the succinimide ester **II-25** was complicated by purification problems. **II-23**, N-hydroxysuccinimide (**II-24**) and dicyclohexylcarbodiimide (DCC) were stirred in glyme at 0^{o}C; however, complete dissolution did not occur. Although the reaction was heterogeneous the insoluble material appeared to change and was assumed to be the insoluble hydrated product of DCC, dicyclohexylurea, DCHU. The mixture was stirred for 48 hours. The DCHU was filtered and the solvent was removed from the filtrate. However, the filtrate contained some of the DCHU and column chromatography (1. EtOH, 2. MeOH) was used to isolate the desired product, **II-25**, a new compound, in a low yield of 39.2 %.

II.2.3 Mono-substituted 1,3-Phenylene-16-crown-5

Two 5-substituted compounds containing the 1,3-phenylene-16-crown-5 moiety have been synthesized (**Figure II-9**). 5-Carbomethoxy-1,3-phenylene-16-crown-5, **II-26**, was hydrolyzed to the carboxylic acid **II-27** in ethanol using sodium hydroxide (4M). The starting material was only 80% pure, but after neutralization with HCl (4M) a white crystalline solid was obtained. The yield was 63.3%. The synthesis of the new succinimide ester **II-29** was conducted at room temperature by reacting the acid **II-27** with N-hydroxysuccinimide (**II-28**) in the presence of DCC in glyme. After work-up a white crystalline solid was obtained in 86.2 % yield. Again **II-28** was used for surface functionalization of poly(propylene imine) dendrimers.

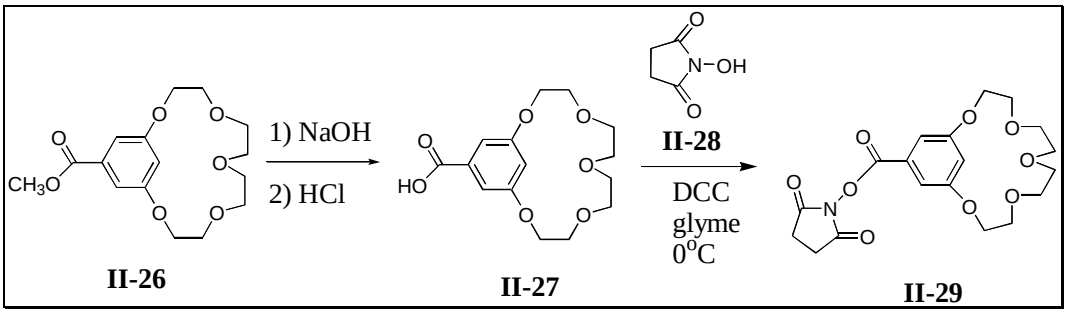


Figure II-9. Synthesis of succinimide ester of 1,3-phenylene-16-crown-5, **II-29**.

II.2.4 Mono-substituted Bis(*meta*-phenylene)-32-crown-10

The synthesis of the mono-methyl ester **II-33** (**Figure II-10**) was conducted in three steps. Resorcinol (**II-13**) was reacted with an excess of tetra(ethylene glycol) dichloride (**II-30**) in the presence of potassium carbonate in a small amount of acetonitrile at 70 ^{o}C for 140 hours. **II-30** was synthesized by reacting tetraethylene glycol with an thionyl chloride. The dichloride precursor product, **II-31**, was purified first by removing the excess of **II-30** by distillation. It was then subjected to liquid-liquid extraction using petroleum ether. The cyclization step was again done using the pseudo-high dilution technique. Methyl-3,5-dihydroxybenzoate (**II-32**) and **II-31** were added slowly (0.60 mL/h) to a mixture of potassium carbonate in DMF. **II-33** was isolated using flash chromatography in a yield of 15.0%.

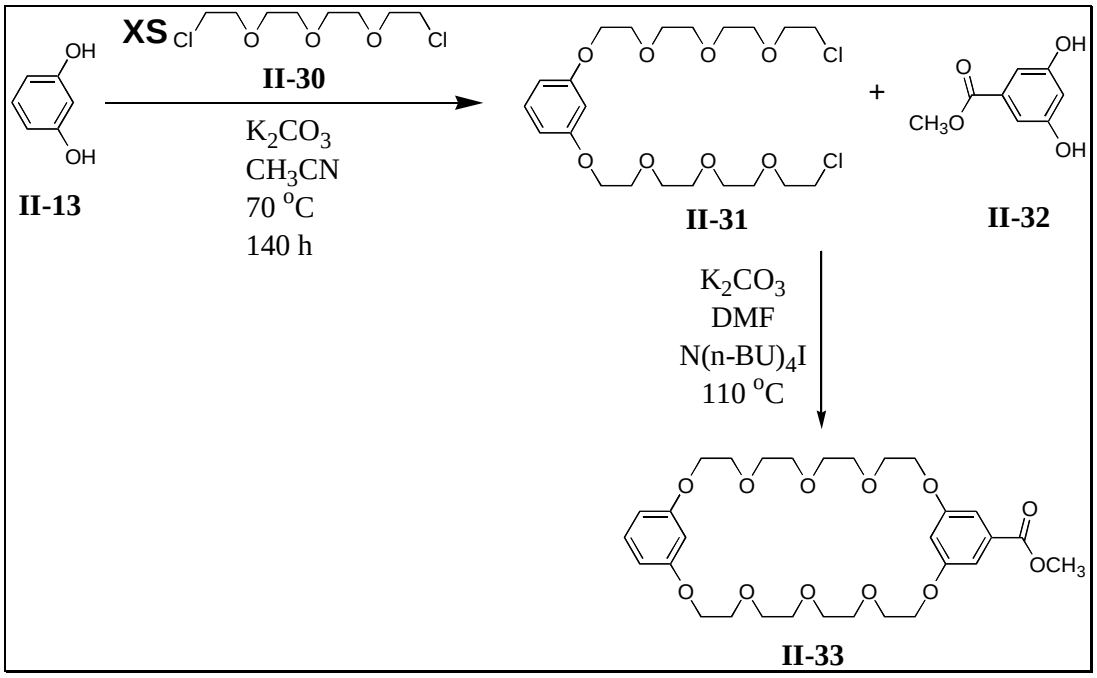


Figure II-10. Synthesis of mono-substituted **BMP32C10**s.

II.2.5 Di-substitued 1,3-Phenylene-20-crown-6

Bis(5-carboxy-1,3-phenylene)-20-crown-6 (**II-37**, **Figure II-11**) was synthesized in several steps. The dichloride **II-35** was synthesized from Bheda's dialcohol **II-34** using an excess of thionyl chloride.[45] The conversion was relatively low (48.1%) as compared to the reported synthesis of the same dichloride from methyl 3,5-dihydroxybenzoate and a large excess of di(ethylene glycol) dichloride (81%).[32] This may be due to the non-homogeneity of the reaction mixture. Two layers were observed upon the addition of thionyl chloride and dissolution did not occur upon heating. The desired product, an oil, was isolated by column chromatography using ethyl acetate.

The diester **II-36** was synthesized under pseudo-high dilution conditions. The dichloride precursor **II-35** was mixed with methyl 3,5-dihydroxy benzoate (**II-32**) in DMF and added slowly (0.60 mL/h) to a suspension of K_2CO_3 in DMF using a syringe pump. The yield of **II-36** was low (27%) when compared to the previously published results (58%).[32] Conversion of the diester **II-36** to the diacid **II-37** was done using tetra-*n*-butyl ammonium hydroxide in ethanol, followed by acidification using 4 molar HCl.

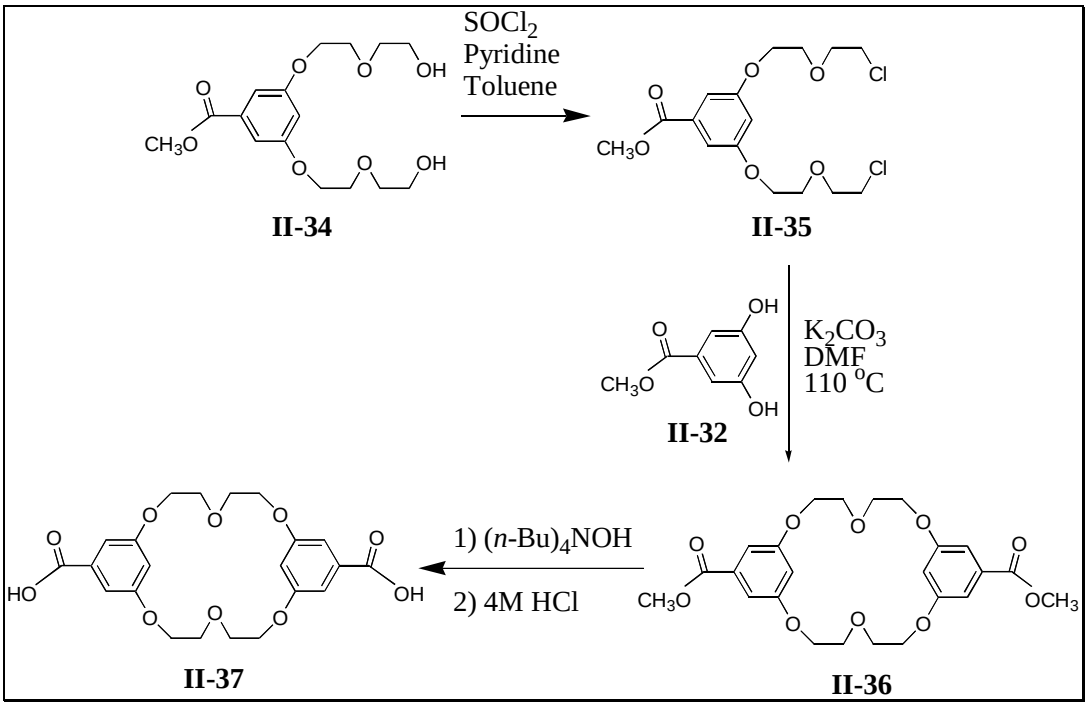


Figure II-11. Synthesis of diacid bis-meta-phenylene-20-crown-6 (**II-37**).

II.2.6 Bis(5-carbomethoxy-1,3-phenylene)-bis(1,4-phenylene)-30-crown-8

The synthesis of the tetraphenylene crown ether bis(5-carbomethoxy-1,3-phenylene)-bis(1,4-phenylene)-30-crown-8 (**II-45**, **Figure II-12**) was not achieved; however, the precursor compounds were made. The syntheses of the intermediates **II-40** through **II-43** were attempted several times and the best yielding reactions are summarized here.

The tetrahydropyran (THP) protected chloride **II-39** was reacted with the benzyl protected phenol **II-38** in the presence of sodium hydride in DMF. The THP group was removed using acid, giving the benzyl protected alcohol **II-40** in a 94.0 % yield. The alcohol **II-40** was converted to the chloride **II-41** in 77.2% yield using thionyl chloride. The synthesis of the diprotected phenol **II-42** was attempted four times using either sodium hydride or potassium carbonate as the base at various reaction temperatures.

Table II-1 compares the yields of the reactions. The best yield (80 %) was obtained using potassium carbonate at 80 ^{o}C. Deprotection of **II-42** to give the diphenol **II-43** was done by hydrogenolysis using palladium (5%/ by wt., wet, Englehard) on carbon at 60 psi. The yield was quantitative.

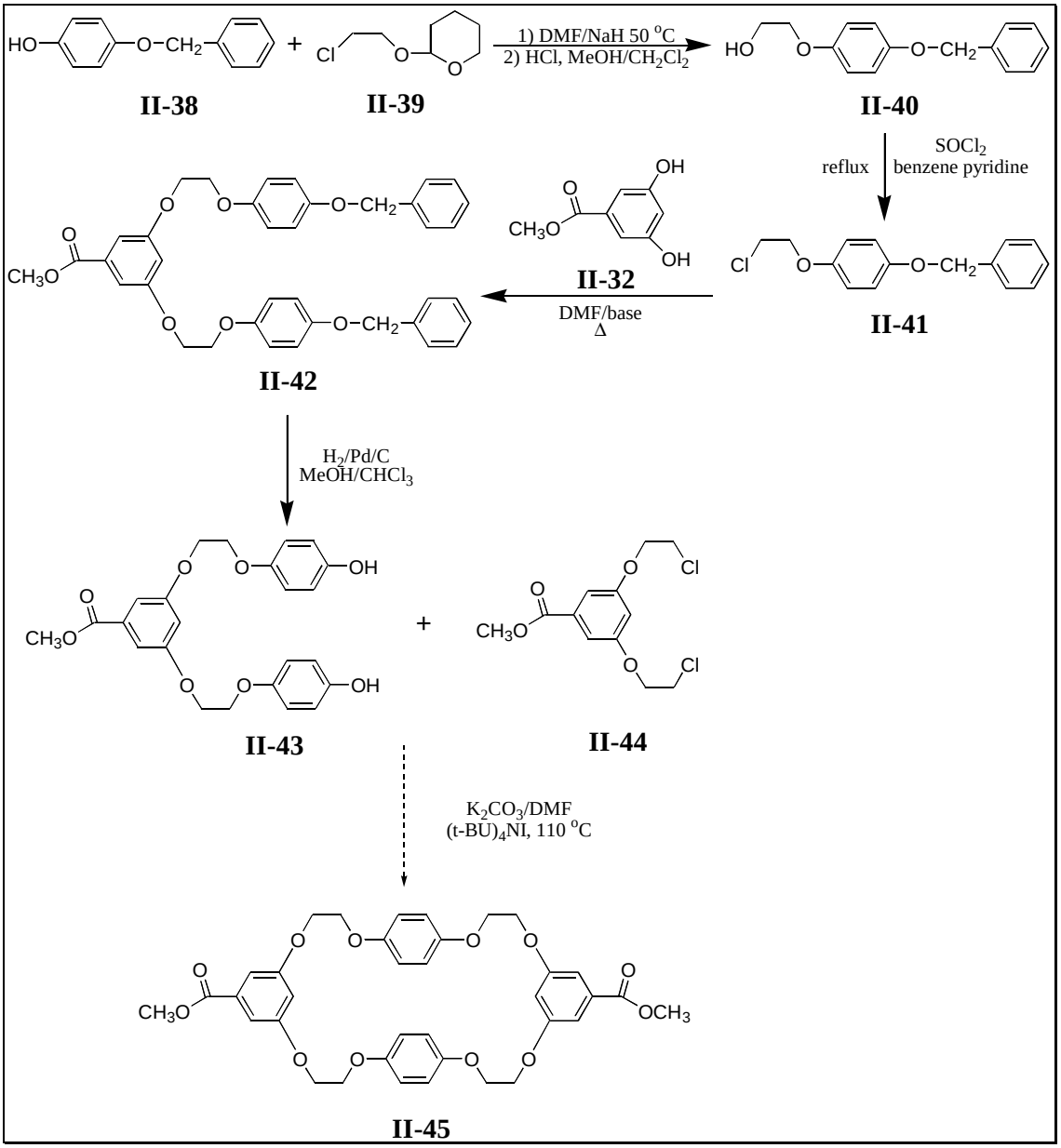


Figure II-12. Attempted synthesis of bis(5-carbomethoxy-1,3-phenylene)-bis(1,4-phenylene)-30-crown-8 (**II-45**).

Table II-1. Yields for the synthesis of **II-46** under different reaction conditions.

Reaction T (^{o}C)	**Base**	**% Yield**
25	NaH	0
70	"	74
110	"	40
80	K_2CO_3	80

The final cyclization step was then attempted. Previously, Devdatt Negvakar attempted the synthesis of the 30-membered crown ether **II-45** using sodium hydride as a base. The desired product was not produced; however, 3,5-bis(vinyloxy)benzoic acid was isolated. Therefore, the synthesis of **II-45** was attempted using the same method with the exception of potassium carbonate as the base. The diphenol **II-43** and dichloride **II-44** were dissolved in DMF and added slowly (0.60 mL/h) to a suspension of potassium carbonate in DMF at 110 °C. The reaction was cooled to room temperature after stirring for seven days. The solvent was removed to give a yellow, viscous oil. Thin-layer chromatography (TLC) using ethyl ether indicated a mixture of several compounds. Column chromatography (ethyl ether) was then used to purify the organics. Several fractions were taken, some of which were not pure. Approximately 15% of the starting material was recovered. The other fractions were analyzed by ^{1}H NMR and did not indicate the presence of the desired product. 3,5-Bis(vinyloxy)benzoic acid was not observed in any of the fractions. Although this vinyl ether was not isolated, its reactivity would be rather high and a crosslinked polymer network could be produced.

II.3 Conclusions

Several crown ethers with either no functionality, mono-functionality, or di-functionality have been synthesized. Although the reactions appear to be simple in design, years of research in our labs have optimized the conditions to improve the overall yields. Some of these improvements were developed during the research summarized above. This allows our group to produce these unique macrocycles in gram quantities. A difficult part of their production is their purification. Since crown ethers have a wide range of solubilities they are difficult to recrystallize. Unfortunately, the best way to purify them currently is by column chromatography. In some cases a Soxlhet extraction can be employed.

Once the crown ethers are made they can be used as building blocks in the formation of supramolecular assemblies and supermolecules. The focus of the thesis uses crown ethers to form complexes with secondary ammonium ions. The complexation phenomena will be discussed in **Chapter VI**.

II.4 Experimental

Chemical Reagents and Measurements

All chemicals were reagent grade and used directly as received from Aldrich except where specified. All solvents were HPLC or GC grade. The glyme was dried by storing it over potassium hydroxide pellets, refluxing in the presence of sodium hydride, and finally fractionally distilling it with a nitrogen purge. THF was dried by refluxing in the presence of sodium metal and benzophenone. **II-44** was previously synthesized by Nagvekar. Melting points were taken in capillary tubes and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on a 400 MHz Varian spectrometer with tetramethylsilane as an internal standard. The following abbreviations have been used in describing NMR spectra: s (singlet), d (doublet), t (triplet), q (quartet), br s (broad singlet), and m (multiplet). Elemental Analyses were performed by Atlantic Microlabs of Norcross, GA.

1. Tri(ethylene) glycol dichloride (II-12): Thionyl chloride was added dropwise to a solution containing tri(ethylene glycol) (**II-11**, 299.3 g, 1.99 mol), pyridine (215 mL), and toluene (1240 mL). A white precipitate was formed prior to heating. The mixture was refluxed for 24 h. TLC indicated the presence of the dichloride product. The product was decanted, and washed with water (3 x 200mL), HCl (2 M, 2 x 100mL), and a saturated solution of NaCl (2 x 100mL). The toluene was removed and the product was distilled twice under reduced pressure (bp = 80-82 ^{o}C at 0.80-0.75 mm Hg, Lit.[70] = 65 ^{o}C at 1 mm Hg). Yield: 303.5 g (81.9 %). ^{1}H NMR (400 MHz, $CDCl_3$, ambient T): δ (ppm) = 3.75 (t, J = 5.6 Hz, 4H, α-CH_2), 3.66 (s, 4H, γ-CH_2-), 3.64 (t, J = 5.6 Hz, 4H, β-CH_2-).

2. 1,3-Bis(8-chloro-3,6-dioxa-1-octyloxy)benzene (II-14): Sodium Hydride (7.92 g, 95%, 330 mmoles) was added in small portions to a stirring solution of resorcinol (**II-13**, 14.92 g, 132 mmoles) in DMF (100 mL). Generation of hydrogen gas was seen upon addition. At the beginning of the addition the solution was clear, but upon the addition of NaH the solution turned milky white, brown, green, and finally purple. After the addition of NaH the solution was stirred for two h at 110 ^{o}C. The Na/resorcinol mixture was

added dropwise (over 4 h) to a solution of tri(ethylene glycol) dichloride (**II-12**, 247 g, 1.32 moles). The resulting solution was stirred and heated at ~50 ^{o}C for seven days. The mixture was filtered over Celite® and the DMF was removed. **II-12** was distilled from the solution (mass = 183 g, bp = 83-85 ^{o}C @ 0.75-1.52 mm Hg). The crude product (52.9 g) was analyzed by TLC (diethyl ether) and showed ~ 7 spots, but not all of the product dissolved in the solvent (diethyl ether). It was readily apparent that resorcinol was present. A 10% potassium carbonate solution was used to extract the left over resorcinol (3 x 100 mL). The resorcinol was removed completely as seen by TLC but three spots were seen. The brown oil was subjected to flash chromatography in diethyl ether and a yellow oil[71] was obtained. Yield: 51.2 g (94.3 %). ^{1}H NMR (400 MHZ, $CDCl_3$, ambient T): δ (ppm) = 7.15 (t, J = 8.4 Hz, 1H, *m*-H), 6.51 (m, 3H, *o*,*p*-H), 4.10 (t, J = 4.8 Hz, 4H, α-CH_2), 3.85 (t, J = 4.8 Hz, 4H, β-CH_2), 3.73 (m, 12H, γ,δ,ε–CH_2), 3.63 (t, J = 4.8 Hz, 4H, ζ-CH_2).

3. Bis(*meta*-phenylene)-26-crown-8 (II-15, **BMP26C8):** A mixture of 1,3-bis(8-chloro-3,6-dioxa-1-octyloxy)benzene (**II-14**, 12.0 g, 29.2 mmoles) and resorcinol (**II-13**, 3.24 g, 29.4 mmoles) in 45 mL of DMF was added to a suspension of K_2CO_3 (40.60 g, 294 mmoles) and tetra-*n*-butylammonium iodide (50 mg) in 1.5 L DMF at 110 ^{o}C. The mixture was added at a rate of 0.75 mL/h under nitrogen flow. The addition was complete after ten days. Several color changes took place during the addition process. The solution turned from clear to brown to green. After the addition the solution was stirred for 5 days at 110 ^{o}C. The DMF was removed by rotoevaporation and a slurry was made with the crude material and silica gel. This slurry was added to a thimble and Soxhlet extraction was performed using ethyl ether. After two days of extraction a TLC of the extraction liquid indicated that there were several impurities as well as the desired macrocycle. The ether was removed and the yellow-orange oil that remained was left in a round bottom flask in the hood. After one day, crystals appeared and analyzed by ^{1}H NMR. The ^{1}H NMR spectra indicated that the crystals were the desired macrocycle. After another day more crystals formed but some yellow-orange oil was also in the

crystals. The product was isolated by recrystallization from ethanol. Yield: 2.83 g (18.1%). Melting point = 102.6 - 103.6 ^{o}C (Lit.[72] = 99 - 101 ^{o}C), ^{1}H NMR (400 MHz, $CDCl_3$, ambient T): δ (ppm) = 7.18 (t, J = 8.2 Hz, 2H, H_a), 6.53 (dd, J = 8.2, 2.3 Hz, 4 H, H_b), 6.45 (t, J = 2.3 Hz, 2H, H_a), 4.06 (m, J = 4.6, 1.83 Hz, 8H, α-CH_2), 3.75 (m, J = 4.6, 1.8 Hz, 8H, β-CH_2), 3.63 (s, 8H, γ-CH_2).

4. 4-Carbomethoxy-dibenzo-24-crown-8 (**II-19**). **Method A**: A solution of the dichloride precursor **II-17** (17.17 g, 41.74 mmol) and methyl-3,4-dihydroxybenzoate (**II-18**, 7.02 g, 41.74 mmol) was made in 50 mL of DMF. The solution was added slowly (0.60 mL/h) to a suspension of K_2CO_3 (86.52 g, 626 mmol) in DMF (2.0 L) at 110 ^{o}C. The mixture was stirred using a mechanical stirrer. After complete addition the reaction mixture was stirred for 7 days. Upon cooling, the mixture was filtered through Celite® and the DMF was removed from the filtrate by rotoevaporation. The resulting brown oil was absorbed onto silica gel. The silica gel was subjected to Soxhlet extraction using ethyl ether for 6 days. The desired product crystallized out and was recrystallized from ethanol. Yield: 7.51 g (35.5 %). **Method B**: To a 5 L, 3 neck Morton flask equipped with a mechanical stirrer, nitrogen inlet, and thermometer were added CH_3CN (3.5 L) and K_2CO_3 (80.60 g, 584 mmol) at 70 ^{o}C. A solution of **II-17** (25.4 g, 61.8 mmol) and **II-18** (10.4 g, 61.8 mmol) in CH_3CN (120 mL) was added via a syringe pump at a rate of 0.75 mL/h. After complete addition the reaction mixture was stirred for 6 days. Upon cooling, the mixture was filtered and the solvent was removed by rotoevaporation. The oil was absorbed onto silica gel and subjected to Soxhlet extraction for 3 days. A yellow oil was obtained from which a white solid precipitated after dilution with MeOH and sitting in a freezer overnight. The solid was recrystallized from EtOH. Yield = 12.67 g (40.3 %). Mp = 82.8 - 84.9 ^{o}C (lit.[44] = 83 - 85 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$, ambient T) δ (ppm): 7.63 (dd, J = 1.6, 8.0 Hz, 1H), 7.51 (d, J = 1.6 Hz, 1H), 6.87 (m, 5H), 4.18 (m, 4H), 4.13 (m, 4H), 3.91 (m, 8H), 3.86 (s, 3H), 3.83 (s, 4H), 3.82 (s, 4H); ^{13}C NMR (100 MHz) δ (ppm): 166.7, 152.8, 148.8, 148.1, 123.8, 122.7, 121.3, 121.3, 114.1, 114.0, 113.9, 111.9, 71.4, 71.3, 71.2, 69.9, 69.7, 69.6, 69.4, 69.3, 69.3, 69.2, 51.9 (23 carbons of 26 expected).

5. O,O-Bis(8-hydroxy-3,6-dioxaoctyl)catechol (II-27). Catechol (**II-16**, 1.63 g, 14.8 mmol) and K_2CO_3 (10.2 g, 74.1 mmol) were stirred in 75 mL of CH_3CN and refluxed for 4 h. To this mixture 2-[2'-(2''-chloroethoxy)ethoxy]ethanol (**II-26**, 5.0 g, 30 mmol) was added dropwise at 70 ^oC. The reaction mixture was then stirred for 140 h at 70 ^oC. The mixture was then vacuum filtered. The solvent was removed by rotoevaporation to give a brown, viscous oil.[73] TLC gave one spot. Yield = 5.54 g (90.4%). ^1H NMR ($CDCl_3$, 400 MHz), δ (ppm): 6.92 (-Ar-, 4H, s), 4.18 (α, 4H, t, J = 4.8 Hz), 3.88 (β, 4H, t, J = 4.8 Hz), 3.68 (γ, 16H, m). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 148.8, 121.7, 114.7, 72.6, 70.7, 70.3, 69.7, 68.7, 61.5 (9 peaks as required).

6. O,O-Bis(8-chloro-3,6-dioxaoctyloxy)catechol (II-17). Method A: O,O-bis(8-hydroxy-3,6-dioxaoctyl)catechol (**II-27**, 4.50 g, 12.0 mmol) was stirred in 50 mL of toluene containing pyridine (3.0 g, 38 mmol). Thionyl chloride (3.57 g, 30 mmol) was added dropwise. The mixture was refluxed for 36 h. The mixture was decanted and the solvent was removed by rotoevaporation to give a slightly yellow oil.[74] Yield = 3.91 g (78.8 %). **Method B**: **II-27** (18.11 g, 164 mmol) and K_2CO_3 (113.3 g, 820 mmol) were stirred in CH_3CN (350 mL) at 70 ^oC in a 1 L 4-neck round bottom flask equipped with a mechanical stirrer, reflux condenser, and a 500 mL addition funnel for 3h. Tri(ethylene glycol) dichloride (**II-12**, 400 g, 2.14 mol) was added dropwise to the mixture over 1 h. The resulting mixture was stirred for 140+ h at 70 ^oC. The procedure was repeated 2 more times. The reactions were combined, filtered, and the solvent was removed by rotoevaporation. Liquid-liquid extraction using petroleum ether was employed for 5 days to isolate a slightly orange oil. Yield =149.9 g (74.0 %). ^1H NMR (400 MHz, $CDCl_3$, ambient T) δ (ppm): 6.92 (m, 4H), 4.18 (m, 4H), 3.87 (m, 4H), 3.70 (m, 16H); ^{13}C NMR (100 MHz) δ (ppm): 149.0, 121.7, 114.9, 71.4, 70.8, 70.7, 69.9, 68.9, 42.8 (9 carbons as expected).

7. **Methyl-3,4-dihydroxybenzoate** (**II-18**): Concentrated H_2SO_4 (10 mL) was added dropwise to a solution of 3,4-dihydroxybenzoic acid (19.32 g, 125.49 mmol) in MeOH

(100 mL). The reaction was heated at reflux for 15h with stirring. Upon cooling the solvent was removed by rotoevaporation and a brown oil was obtained. The oil solidified upon standing. The brown solid was recrystallized from water and dried under vacuum for 24 h. Yield = 15.99 g (75.9 %). mp = 139.5 - 141.0 ^{o}C (lit.[75] = 138.5 - 139.5 ^{o}C). ^{1}H NMR (400 MHz, DMSO-d_6, ambient T) δ (ppm) 3.78 (s, 3H), 6.83 (d, J = 8.0 Hz, 1 H), 7.34 (dd, J = 8.0, 2.4 Hz, 1H), 7.38 (d, J = 2.4 Hz, 1H), 9.46 (s, 1H), 9.87 (s, 1H); ^{13}C NMR (100 MHz) δ (ppm): 51.5, 115.3, 116.2, 120.5, 121.8, 145.0, 150.3, 166.2 (8 carbons as expected).

8. 2-[2'-(2''-Chloroethoxy)ethoxy]ethanol (II-26): In a 1 L round bottom flask equipped with a mechanical stirrer, reflux condenser, and a nitrogen bubbler, $SOCl_2$ (23.0 mL, 316 mmol) was added dropwise over a period of 6 h to a solution of triethylene glycol (47.46 g, 316 mmol) and pyridine (24.4 mL, 302 mmol) in toluene (500 mL). The reaction mixture was then heated at reflux for 20h. Upon cooling the solution was decanted and the pyridine salt was washed with toluene. The toluene was removed by rotoevaporation to give a dark brown oil. The oil was dissolved in deionized H_2O and extracted with toluene (3 x 100 mL). The aqueous layer was rotoevaporated and the resulting yellow oil was dissolved in a saturated NaCl solution. The solution was extracted with ethyl ether. Rotoevaporation of the ether gave a clear oil.[76] Yield: 22.40 g (42.0%). ^{1}H NMR (400 MHz, $CDCl_3$, ambient T) δ (ppm): 3.75 (m, 4H), 3.69 (s, 4H), 3.64 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, ambient T) δ (ppm): 72.4, 71.1, 70.4, 70.1, 61.4, 42.5 (6 peaks as required).

9. 4-Hydroxymethyldibenzo-24-crown-8 (**II-20**): Lithium aluminum hydride (LAH, 11.5 mL of 1.0 M THF sol., 11.5 mmol) was added to a solution of 4-carbomethoxydibenzo-24-crown-8 (**II-19**, 10.00 g, 19.7 mmol) in anhydrous THF (600 mL) in a 3-neck, 1 L round bottom flask equipped with a mechanical stirrer and nitrogen inlet. The mixture was stirred overnight. Ethyl acetate was added to neutralize the excess LAH. Water (~100 mL) followed by 10% HCl was added until the solution was no longer

cloudy. The solution was washed with ethyl ether (3 x 200 mL). Evaporation of the organic layer gave a white solid which was recrystallized from ethanol. Yield = 8.88 g (94.2 %). Mp = 79.1 - 81.7 ^{o}C (lit.[41] = 82.3 - 84.7 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, ambient T) δ (ppm):3.83 (s, 8H), 3.91 (t, J = 4.4 Hz, 8H), 4.13 - 4.17 (m, 8H), 4.58 (s, 2H), 6.82 - 6.90 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$, ambient T) δ (ppm): 65.2, 69.4, 69.5, 69.9, 71.3, 112.9, 113.8, 114.0, 119.9, 121.4, 134.2, 148.4, 148.9, 149.0 (14 peaks of 16 expected).

10. Isonicotinic Ester of 4-hydroxymethyldibenzo-24-crown-8 (**II-22**): In a 3-neck round bottom flask equipped with a reflux condenser, gas bubbler, and two stopcock inlets (one with a septum), isonicotinic acid (0.406 g, 3.30 mmol) was stirred in excess thionyl chloride (25 mL) for 1 h, at which point dissolution occurred. The resulting solution was heated at reflux for 1 additional h. Upon cooling the excess thionyl chloride was removed by vacuum distillation using a water aspirator. To the resulting slightly yellow solid was added a pyridine (5 mL) solution of **II-20** (1.60 g, 3.34 mmol) via syringe and the solution was heated at reflux for 17 h. Upon cooling a white precipitate was observed. To the mixture was added water (~75 mL) and ethyl ether (~75 mL). The organic layer was washed several times with water (2 x 75 mL). Removal of the solvent from the organic layer gave the desired product as a white solid. The product was recrystallized from ethanol. Yield = 1.79 g (93.2 %). Mp = 106.3 - 107.2 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, ambient T) δ (ppm): 3.83 (s, 8H), 3.91 (m, 8H), 4.16 (m, 8H), 5.28 (s, 2H), 6.85 - 6.91 (m, 5H), 6.95 - 7.00 (m, 2H), 7.84 (d, J = 6.0, 2.0 Hz, 2H) 8.77 (d, J = 6.0, 2.0 Hz). EA (found, calculated): C 63.63, 63.80; H 6.47, 6.39.

11. 4-Carboxydibenzo-24-crown-8 (**II-23**): In a 2-neck 250 mL round bottom flask equipped with a reflux condenser, nitrogen bubbler, and magnetic stir bar 4-carbomethoxydibenzo-24-crown-8 **(II-19**, 1.99 g, 3.93 mmol) was suspended in ethanol (100%, ~100 mL). A 1 M solution of KOH (5 mL) was added and dissolution occurred. The reaction was heated at reflux for a few minutes and then cooled to RT. Thin layer

chromatography (ethyl acetate) indicated the starting material was gone. The solvents were removed by rotoevaporation to give a yellow oil. The oil was dissolved in water and 70% H_2SO_4 was added dropwise until a white precipitate was observed. Once the mixture was acidic the solid was filtered and washed with water. The white solid was recrystallized from chloroform/hexanes. Yield = 1.89 g (97.4 %). Mp = 182.5 - 184.5 ^oC (lit.[44] = 182 - 183 ^oC). ^1H NMR (400 MHz, $CDCl_3$, ambient T) δ (ppm): 3.85 (d, J = 2.8 Hz, 8H), 3.94 (m, 8H), 4.15 (t, J = 4.4 Hz, 4H), 4.20 (m, 4H), 6.88 (m, 5H), 7.56 (d, J = 1.6 Hz, 1H), 7.71 (dd, J = 1.6, 8.4 Hz, 1H).

12. Succinimide ester of 4-carboxydibenzo-24-crown-8 (**II-25**): 4-carboxy-dibenzo-24-crown-8 (**II-23**, 1.34 g, 2.73 mmol) and N-hydroxysuccinimide (0.323 g, 2.81 mmol) were dissolved in 50 mL of glyme. To this stirring solution dicyclohexylcarbodiimide (0.620 g, 3.00 mmol) was added at 0 ^oC. Complete dissolution did not occur, but the appearance of the white solid in the solution did change. The mixture was stirred for 48 h. The precipitate was filtered under vacuum and washed with $CHCl_3$. The solvent was removed from the filtrate by rotoevaporation to give a white oil. The oil was dissolved in hot isopropyl alcohol and upon cooling a white powder was obtained. The solid was purified by column chromatography (SiO_2, 1. EtOH, 2. MeOH). It was recrystallized from isopropyl alcohol. Yield = 0.631 g, (39.2%). Mp = 81 - 90 ^oC. ^1H NMR (DMSO-d_6, 400 MHz), δ (ppm): 7.71 (H_3, 1H, d, J = 8.8 Hz); 7.48 (H_2, 1H, s); 7.71 (H_4, 1H, d, J = 8.8 Hz), 6.89 (H_{Ar}, 4H, m); 4.21 (α, 4H, m); 4.15 (α', 4H, m); 4.05 (ζ, ζ', 8H, m); 3.77 (β, β', ε, ε', 16H, m); 3.66 (δ, δ', γ, γ', 16H, m); 2.87 (H_1, 4H, s). ^{13}C NMR (DMSO-d_6, 100 MHz), δ (ppm): 170.4, 161.3, 157.8, 154.3, 148.4, 148.3, 148.2, 124.8, 121.1, 116.2, 114.0, 113.9, 113.8, 112.8, 70.55, 70.47, 70.40, 69.2, 69.13, 69.0, 68.9, 68.74, 68.69, 68.66, 25.5. EA (found, calculated): C 59.11, 59.08; H 6.08, 5.98.

13. 5-Carboxy-1,3-phenylene-16-crown-5 (II-27): 5-Carbomethoxy-1,3-phenylene-16-crown-5 (**II-26**, 4.6 g of ~80% pure) was dissolved in 150 mL of ethanol. 4M NaOH (50 mL) was added and the resulting solution was heated at reflux while stirring for 24 h.

Upon cooling to room temperature, 4M HCl was added until the solution was acidic. A white precipitate was observed. Upon removal of the solvent by rotoevaporation, the resulting yellow solid was dissolved in deionized water and extracted with chloroform. The chloroform was removed by rotoevaporation to give a yellow oil. The yellow oil solidified upon trituration with hexanes. The resulting solid was filtered and recrystallized from ethanol. Yield = 2.33 g (63.3 %). Mp = 135.1 - 139.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ambient T), δ (ppm): 7.37 (t, 1H, J = 2.8 Hz), 7.27 (d, 2H, J = 0.8 Hz), 4.33 (t, 4H, J = 4.6 Hz), 3.81 (t, 4H, J = 4.6 Hz), 3.63 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$, ambient T), δ (ppm): 170.8, 160.2, 130.6, 111.7, 109.9, 70.7, 70.7, 70.4, 69.0 (9 peaks as required). Elemental analysis for $C_{22}H_{24}O_6$ (calculated, found): C, 58.93, 58.84; H, 5.39, 5.47.

14. Succinimide Ester of 5-carboxy-1,3-Phenylene-16-crown-5 (**II-29**): 5-carboxy-1,3-phenylene-16-crown-5 (**II-27**, 2.087 g, 6.68 mmol) and N-hydroxysuccinimide (**II-28**, 0.792 g, 6.88 mmol) were dissolved in 30 mL of glyme. To this stirring solution dicyclohexylcarbodiimide (1.516 g, 7.35 mmol) was added at 0 °C. The solution was stirred for 24 h. A white precipitate was filtered under vacuum and washed with $CHCl_3$. The solvent was removed from the filtrate by rotoevaporation to give a slightly yellow oil. The oil was dissolved in hot isopropyl alcohol and upon cooling a white powder was obtained. It was recrystallized from isopropyl alcohol twice. Yield = 2.36 g (86.2%). Mp = 112.0 - 115.3 °C. ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.43 (H_3, 1H, m); 7.29 (H_2, 2H, d, J = 1.2 Hz); 4.33 (α, 4H, m); 3.80 (β, 4H, m); 3.62 (γ and δ, 8H, m); 2.90 (H1, 4H, s). ^{13}C NMR (DMSO-d_6, 100 MHz), δ (ppm): 170.7, 160.8, 126.1, 110.8, 110.6, 70.5, 70.3, 70.1, 68.8, 26.0 (10 peaks of 11 expecxted). EA (found, calculated): C 55.68, 55.74; H 5.78, 5.66.

15. Tetra(ethylene glycol) dichloride (II-30): Tetraethylene glycol (300 g, 1.54 mol) was dried by stirring over molecular seives. Thionyl chloride (459.3 g, 3.86 mol, 2.5 equiv.) was added slowly dropwise to mixture of pyridine (which was distilled over CaH,

206.6 g, 2.61 mol) in toluene (1200 mL). The mixture was refluxed for 24 h. Upon cooling, the salt was filtered and the solvent was removed from the filtrate by rotoevaporation. The resulting oil was dissolved in chloroform and washed with water. The product was then isolated by vacuum distillation (103 - 110 ^{o}C, 0.5 - 0.7 mmHg, lit.[77] 106 - 108 ^{o}C, 0.1 mmHg). Yield = 323.5 g (90.6%). ^{1}H (400 MHz, ambient T, $CDCl_3$) δ (ppm): 3.68 (t, J = 6.0 Hz, 4H), 3.59 (s, 8H), 3.55 (t, J = 6.0 Hz, 4H); ^{13}C NMR (100 MHz, ambient T, $CDCl_3$) δ (ppm)**:** 71.3, 70.6, 42.7.

16. 5-carbomethoxy-1,3-phenylene-1',3'-phenylene-32-crown-10 (II-33):

K_2CO_3 (17.083 g, 420.4 mmol) was suspended in DMF (2.5 L) in a 3-neck round bottom flask (3 L) equipped with a mechanical stirrer, reflux condenser, nitrogen bubbler, and a thermometer. $(n\text{-}Bu)_4NI$ (150 mg) was then added and the reaction was heated to 110 ^{o}C with stirring. Methyl-3,5-dihydroxybenzoate (**II-32**, 7.06 g, 42.04 mmol) and the dichloride **II-30** (21.00 g, 42.04 mmol) were dissolved in 100 mL of DMF. To the round bottom flask the mixture was added slowly (0.60 mL/h). After the addition was completed the reaction was stirred at 110 ^{o}C for 7 days. The final suspension was filtered to remove the salt. The DMF was removed by rotoevaporation and the resulting brown oil was absorbed onto silica gel. Flash chromatography (EtOAc) was employed to isolate the final product. The white product was recrystallized from EtOH. Yield = 3.75 g (15.0 %). mp = 70.3 - 72.5 ^{o}C (lit.[33] = 74.8 - 75.4 ^{o}C). ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 7.17 (H_1, 2H, d, J = 2.0 Hz); 7.12 (H_3, 1H, t, J = 8.4 Hz); 6.70 (H_2, 1H, t, J = 2.0 Hz); 6.48 (H_{Ar}, 3H, m); 4.11 (α', 4H, t, J = 5.2 Hz); 4.07 (α', 4H, t , J= 5.2 Hz); 3.88 (-CH_3, 3H, s); 3.84 (β, β', 8H, m); 3.70 (δ, δ', γ, γ', 16H, m). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 166.8, 159.9, 159.7, 131.8, 129.7, 108.0, 107.1, 106.7, 101.6, 70.85, 70.81, 70.76, 69.6, 69.5, 67.8, 67.4, 52.2.

17. Methyl 3,5-bis(5-chloro-3-oxapentyloxy)benzoate (II-35): Methyl 3,5-bis(5-hydroxy-3-oxapentyloxy)benzoate[45] (**II-34**, 9.03 g, 26.2 mmoles), pyridine (6.49 mL), and toluene (37.3 mL) were placed in a 100 mL four-neck round bottom flask equipped

with a reflux condensor, magnetic stir bar and a pressure equilibrating addition funnel. Thionyl chloride (4.8 mL, 7.80 g, 65.6 mmole) was added dropwise over 1h. The resulting heterogeneous mixture was refluxed for 24 h. The solution was filtered upon cooling and washed with toluene. The desired product, an oil,[32,45] was isolated using a short column (EtOAc). Yield = 4.81 g (48 %). ^{1}H NMR (400 MHz, $CDCl_3$, ambient T), δ (ppm): 7.21 (2H, d, J = 2.2 Hz), 6.53 (1H, t, J = 2.2 Hz), 4.16 (4H, t, J = 4.6 Hz), 3.88 (7H, m), 3.83 (4H, t, J = 5.8 Hz), 3.66 (4H, t, J = 5.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ambient T), δ (ppm): 166.6, 159.6, 131.9, 108.0, 106.9, 71.5, 69.5, 67.7, 52.2, 42.6 (10 peaks as required).

18. Bis(5-carbomethoxy-1,3-phenylene)-20-crown-6 (II-36): In a 3 L three-neck Morton flask, DMF (750 mL), K_2CO_3 (5.12 g, 126 mmoles), and (*n*-Bu)$_4$NI (~50 mg), were added. The flask was equipped with a thermometer, reflux condenser, and a mechanical stirrer. Nitrogen flow was also applied. The solution was heated to 110 °C and stirred vigorously. **II-35** (4.81 g, 12.6 mmoles) and methyl 3,5-dihydroxy benzoate (**II-32**, 2.12 g, 12.6 mmoles) were dissolved in ~ 30 mL of DMF and the solution was added via a syringe pump at a rate of 0.60 mL/h. The solution was stirred for 2.5 days. TLC indicated that the reaction was complete. The solvent was then removed by rotoevaporation. The product was isolated using column chromatography (SiO_2, ethyl ether). More product was obtained after Soxhlet extraction using $CHCl_3$. Yield = 1.60 g (27.0 %). mp = 179.3 - 182.5 °C (lit. mp = 179-181 °C[32]). ^{1}H NMR (400 MHz, $CDCl_3$, ambient T), δ (ppm): 7.09 (4H, d, J = 2.4 Hz), 6.67 (2H, brs), 4.12 (8H, brs), 3.83 (14 H, br s). ^{13}C NMR (100 MHz, $CDCl_3$, ambient T), δ (ppm): 166.7, 159.7, 131.7, 108.3, 69.7, 68.0, 52.16 (7 peaks as required).

19. Bis(5-carboxy-1,3-phenylene)-20-crown-6 (II-37): II-36 (1.25 g, 2.62 mmoles) was added to 150 mL of EtOH (100%). Tetra-*n*-butylammonium hydroxide (50 mL, 40% wt. solution in water) was then added. The mixture was stirred with a magnetic stirrer and heated at reflux for 24 h. Upon cooling the solution in ice 4M HCl (50 mL)

was added. A white precipitate was observed. The solid was filtered and recrystallized from pyridine. Yield = 0.822 g (70.0 %). Mp = 310 °C (dec.).[34] ^{1}H NMR (400 MHz, DMSO-d_6, ambient T), δ (ppm): 12.4-13.5 (-COOH, br s), 7.03 (4H, d, J = 1.0 Hz), 6.67 (2H, m), 4.13 (8H, d, J = 2.0 Hz), 3.79 (8H, d, J = 2.0 Hz). ^{13}C NMR (100 MHz, DMSO-d_6, ambient T), δ (ppm): 167.3, 160.0, 133.1, 107.9, 69.4, 68.2 (7 peaks as required). EA (found, calculated): C 58.89, 58.93; H 5.46, 5.39.

20. *p*-(2-Hydroxyethoxy)benzyloxybenzene (II-40): NaH (1.84 g, 46.0 mmol, 1.15 equiv.- 60% in mineral oil) was added slowly to a solution of *p*-benzyloxyphenol (**II-38**, 8.00 g, 40.0 mmol) in DMF (60 mL). The solution was heated at 50 ^{o}C and the THP protected chloroethanol (**II-39**, 7.50 g, 45.6 mmole, Fluka) was added dropwise and the resulting solution was stirred for 30 h. The salt was removed by vacuum filtration. DMF was removed by rotoevaporation to give a yellow-orange oil. A 6:2 methanol:dichloromethane solution containing HCl (5 mL) was added to the oil and stirred for 6 h. The solvents were removed and the resulting mixture was diluted with H_2O. The desired product was extracted with ethyl acetate and recrystallized from heaxanes/ethyl acetate to give white needles. Yield = 9.17 g, (94.0%). Mp = 104.1 - 106.0 ^{o}C (lit.[45] = 104.2 - 106.0 ^{o}C, lit.[78] mp = 103.5 - 104.5 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$, ambient T) δ (ppm): 7.37 (m, 5H, H_f), 6.88 (AB q, J = 9.2 Hz, 4H, H_c and H_d), 5.02 (s, 2H, H_e), 4.03 (t, J = 4.4 Hz, 2H, H_a), 3.93 (m, 2H, H_b), 2.05 (t, J = 6.4 Hz, 1H, -OH). ^{13}C NMR (400 MHz, $CDCl_3$, ambient T) δ (ppm): 61.57, 69.82, 70.66, 115.53, 127.44, 127.88, 128.54, 137.18, 152.93, 153.28 (11 peaks as required).

21. *p*-(2-Chloroethoxy)benzyloxybenzene (II-41): Pyridine (11.9 mL, 147 mmol, 2.4 equiv.) was added to a solution of **II-39** (15.00 g, 61.4 mmol) in benzene (300 mL). Thionyl chloride (17.54 g, 147 mmol) was added dropwise to the mixture. The suspension was heated at reflux for 48 h. The resulting yellow liquid was decanted and the desired product was washed in benzene using H_2O, dilute HCl, and a H_2O-NaCl saturated solution. The yellow, tacky solid obtained was recrystallized from hexanes to

give the desired product. Mp = 75.4 - 76.5 ^{o}C (lit.[45] = 69.7 - 71.2 ^{o}C). Yield = 12.46 g (77.2 %). ^{1}H NMR (400 MHz, $CDCl_3$, ambient T) δ (ppm): 7.36 (m, 5H, H_f), 6.87 (AB q, J = 9.2 Hz, 4H, H_c and H_d), 5.01 (s, 2H, H_e), 4.17 (t, J = 5.8 Hz, 2H, H_a), 3.77 (t, J = 5.8 Hz, 2H, H_b). ^{13}C NMR (400 MHz, $CDCl_3$, ambient T) δ (ppm): 42.01, 68.84, 70.63, 115.88, 115.94, 127.45, 127.91, 128.54, 137.14, 152.48, 53.51 (11 peaks as required).

22. Methyl 3,5-bis[2-(*p*-benzyloxyphenoxy)ethoxy]benzoate (II-42): Potassium carbonate (4.20 g, 31.0 mmol, 5.0 equiv.) was stirred with methyl 3,5-dihydroxybenzoate (**II-32**, 1.02 g, 6.07 mmol) in DMF (~60 mL) for 1h at 120 ^{o}C. *p*-(2-Chloroethoxy)benzyloxybenzene (**II-41**, 3.30 g, 12.6 mmol) was added to the solution at 80 ^{o}C. The resulting solution was stirred for 46h. The salt was removed by filtration with Celite®. Trituration with heaxanes gave a brownish solid which was recrystallized from hexanes:EtOAc. Mp = 105.4 - 107.5 °C (lit.[45] = 79.4 - 81.7 ^{o}C). Yield = 80.0 % (3.0 g). ^{1}H NMR (400 MHz, DMSO-d_6, ambient T), δ (ppm): 7.43 (m, 4H), 7.38 (m, 4H), 7.32 (m, 2H), 7.12 (s, 2H), 6.93 (m, 9H), 5.04 (s, 4H), 4.34 (d, 4H, J = 4.2 Hz), 4.24 (d, 4H, J = 4.2 Hz), 3.84 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, ambient T), δ (ppm): 166.3, 160.0, 153.0, 152.9, 137.8, 132.1, 128.8, 128.1, 128.0, 116.2, 115.9, 108.1, 106.8, 70.1, 67.4, 67.1, 52.7 (17 peaks as required).

23. Methyl 3,5-bis[(2-(*p*-hydroxyphenoxy)ethoxy]benzoate (II-43): II-42 (2.50 g, 4.03 mmole) was dissolved in a 50:50 mixture of MeOH and $CHCl_3$ in an hydrogenation flask. Palladium catalyst on carbon (800 mg, 5%, wet, Englehard) was added to the flask and it was pressurized with hydrogen gas (60 psi). After 6 days the mixture was filtered and the solvent was removed. A yellow oil was obtained. The oil was triturated with chloroform to give a solid, which was recrystallized from hexanes/EtOAc. Mp = 127.6 - 130.0 ^{o}C (lit.[45] = 130.3 - 131.9 ^{o}C) Yield = 1.78 g (100 %). ^{1}H NMR (400 MHz, DMSO-d_6, ambient T) δ (ppm): 8.94 (-OH, brs), 7.11 (2H, 2.4 Hz), 6.90 (1H, t, J = 2.4 Hz), 6.79 (4H, m), 6.68 (4H, m), 4.32 (4H,m), 4.19 (4H, m), 3.84 (3H, s). ^{13}C NMR (100

MHz, DMSO-d_6, ambient T), δ (ppm): 52.21, 66.58, 66.89, 106.20, 107.48, 115.38, 115.65, 131.55, 150.92, 151.31, 159.51, 165.72 (12 peaks as required).

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